Evidence is presented which suggests that the sample is adequate for the results to be considered as an accurate reflection of the total tuberculous infection in the community.

The trend of conversion rates at different age groups in the Rhondda Fach and in another valley are presented. These form a satisfactory basis for later comparison applicable to the studies which are to be continued in the future to ascertain the effect of the control of tuberculous infectivity in the Rhondda Fach.

Possible sources of error have been considered, including that of error in the qualitative reading of tuberculin tests by experienced observers, and none of these are regarded as invalidating the results and purpose of the survey.

A comparability study was carried out in 692 cases between the multiple-puncture method of tuberculin-testing and the normal intradermal method. The inclusion of figures obtained by the use of the multiple-puncture method of testing does not invalidate the results or conclusions drawn from the study. As yet the multiple-puncture test cannot be regarded as a satisfactory single test for survey work requiring scientific accuracy.

Evidence is presented that the criterion of 5 mm. of induration for the reading of a positive test with 0.01 mg. of O.T. is probably too high.

I am grateful to Dr. V. W. J. Hetreed for his ready co-operation in the work on double-observer reading of the tests and to Mr. John H. Phillips, Administrative Officer of the Mass Radiography Service in Wales, for the organization of the survey and in the preparation of the statistical tables. I am indebted to the Medical Research Council, London, for the material and equipment used in this study and to the Cardiff Public Health Laboratory for its preparation and sterilization; to Professor F. Heaf, of the Department of Tuberculosis in the Welsh National School of Medicine, to Dr. Norman Tattersall, late Regional Tuberculosis Physician, Welsh Regional Hospital Board, to Mr. Peter Oldham and Dr. A. L. Cochrane, of the Pneumoconiosis Research Unit, and to Dr. J. B. Atkins, H.M. Inspector of Mines, for generous and helpful criticism.

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Dr. Max J. Miller, of the Institute of Parasitology, McGill University, has recently been appointed Research Director of the Liberian Institute of the American Foundation for Tropical Medicine. The Foundation was incorporated in 1934, and is associated with the American Society of Tropical Medicine and the American Academy of Tropical Medicine. The Foundation supports the teaching of tropical medicine in medical schools and promotes research into tropical disorders. The Liberian Institute was established in 1946 to carry on comprehensive research on the origins, treatment, and control of tropical diseases. The Institute's immediate objective is to provide an international laboratory centre where medical, governmental, educational, and industrial scientists of all nationalities can unite in a common attack on diseases of man and domestic animals, and on the production of balanced food crops for both man and animals.

CHLORAMPHENICOL TREATMENT OF THE NEWBORN

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The synthesis and large-scale production of chloramphenicol has made available everywhere a valuable antibiotic, effective against a wide range of pathogenic organisms, including strains resistant to penicillin. As the drug can be taken by mouth, vast numbers of patients, old and young, have been treated somewhat empirically, and it is not surprising that some of the hundreds of papers describing successful therapy disclose serious toxic effects. Most of the reports of fatal aplasia of bone marrow are associated with relatively large doses, or prolonged or repeated treatment with the drug (Hawkins and Lederer, 1952; Sturgeon, 1952; Smiley *et al.*, 1952; Claudon and Holbrook, 1952; Wolman, 1952).

It has therefore become necessary that the clinician should know exactly what serum concentration to expect from a recommended dose. In the case of adults this was provided by Ley *et al.* (1948) and by Hewitt and Williams (1950). For children, Kelly *et al.* (1951) have reported blood-serum levels, and shown how long they persist. As their series contained only one baby less than 6 kg. in weight, an investigation was undertaken in order to establish serum levels obtained in babies during the first fortnight of life.

A group of babies suffering from staphylococcal infections was therefore selected for trial with chloramphenicol therapy.

Present Investigation

Methods.—Blood was obtained in sterile Wright's capillaries from heel puncture. With this method quite small quantities of blood yielded enough serum for assay.

Assay.—Numerous different organisms have been used for the biological assay of chloramphenicol levels in blood serum. The organism most commonly recommended is *Sh. sonnei*. We have tested various other bacteria and found that, using the capillary technique of Fleming (1944), one of our strains of Group A beta-haemolytic streptococci (9570) was conveniently inhibited by exactly 1 µg. of chloramphenicol per ml. The use of this strain clearly simplified the estimation of chloramphenicol levels when a result in µg. per ml. of serum was required.

Test.—The results were read after incubation at 37° C. overnight, the end-point being the tube in which the test organism just failed to grow. This was confirmed by Gram-staining where there was any doubt.

Dosage of Drug.—In order to ensure that all of the intended dose was taken by the babies, chloramphenicol was dispensed as a powder, each powder being made up separately in a waxed paper packet, according to the infant's weight. The powder was given by teaspoon, together with a small amount of syrup. By the dosage scheme, only a limited series of weighed powders need be held by the dispensary to meet the requirements of babies of different sizes, and powders of appropriate amount were available at all times of the day and night. As will be seen from the Table, even at the extremes of each weight range the

deviation from the intended dose is very slight. This dosage was calculated on the basis of 100 mg. per lb. (220 mg. per kg.) per day in three separate doses.

As babies do not appear to taste chloramphenicol it was not thought necessary to use the palmitate derivative, the absorption of which might be less certain in the newborn.

Chloramphenicol Dosage According to Weight

Weight of Baby	Individual Dose
1½ lb. (0.68 kg.) and below	50 mg.
2-3 lb. (0.91-1.36 kg.) inclusive	100 "
3½-4½ lb. (1.59-2.04 kg.)	150 "
5-6 lb. (2.27-2.72 kg.)	200 "
6½-7½ lb. (2.95-3.40 kg.)	250 "
8-9 lb. (3.63-4.08 kg.)	300 "

Where the weight lay between the points on the range, it was taken to the nearest ½ lb., and doubtful ones were placed in the higher group: thus a 7 lb. 10 oz. (3.46 kg.) baby received 250 mg., and a 7 lb. 12 oz. (3.51 kg.) baby received 300 mg. The chloramphenicol was dispensed as a powder.

Results

A preliminary series of tests was made in 17 babies (weight 6 to 9½ lb.—2.7 to 4.3 kg.) to determine the effect of a constant dose of chloramphenicol (100 mg. thrice daily) irrespective of weight. This method was tried, as

CHART: Serum chloramphenicol levels in 24 newborn babies.

Murray and Crawford (1951) had found that with oral penicillin in the newborn a constant dose of 100,000 units gave excellent serum levels for more than six hours. The results with a constant dose of chloramphenicol gave very inconsistent serum levels, and this method was abandoned in favour of dosage by weight.

The serum level of chloramphenicol was traced over a period of 24 hours in 30 babies who received a single dose according to the scheme shown in the Table. In order to exclude the possible presence of inhibitory substances in the serum, in the first half of the cases a control test was made before administration of the drug. In none of these was any inhibitory level found.

In 24 babies chloramphenicol was detected in the serum, whereas in six no serum level was found. In one of these six cases the baby vomited within 30 minutes of receiving the drug, but in the remaining five the causes of the failure to detect a serum level were never elucidated, and in the absence of vomiting must remain open to conjecture, since there is no evidence of failure to absorb the drug. In fact, in one of the five cases the baby received a repeat dose the following day, and levels of 3 µg. were found at one hour, and 6 µg. at seven and a quarter hours after the dose.

It is interesting to note that in Case 30 vomiting occurred one and a quarter hours after the drug was given, and a good serum level was still present at 18 and 24 hours.

The results of these estimations are shown as points in the Chart, and the limits within which they fall appear as a stippled area, which it can be seen forms a smooth curve.

On account of the times at which samples were collected, a calculated mean curve is not presented: it is felt that the band showing the general limits of chloramphenicol levels presents a more useful indication of the results that can be expected from treatment with this drug. Individual cases were followed through, and conformed to the general shape of the curve.

Of the results on the 24 babies shown in the Chart, the first 12 were tested two or three times during the first eight hours in order to establish how rapidly the serum level rose. The remaining cases were used to determine how well the serum level was maintained during the latter part of a 24-hour period. In this group, samples were taken three times—the first at one hour, and the others between 12 and 24 hours after the dose. In only one case in which the chloramphenicol was shown to have been absorbed did the level fall below 4 µg. per ml. serum in under 14 hours.

Discussion

The effect of an antibiotic upon an organism in the body compared with its effect in the test-tube is always a matter of experience and prolonged trial. As this investigation was designed to show the effect of a single dose, no attempt was made to correlate the serum levels with clinical results. However, treatment has proved uniformly satisfactory in cases subsequently treated according to this dosage scheme. The results, however, do show that it is possible to achieve a concentration of chloramphenicol in the serum four to eight times that which is effective in the test-tube. The

Chart shows that in the present series such a level was maintained in almost all cases for more than 12 hours. It would appear, therefore, that for the newborn it should be necessary to give chloramphenicol only in the doses here suggested, twice daily. With any drug given by mouth there is always some risk that it will not be absorbed; this is especially true of babies, for extra care must be taken to ensure that regurgitation does not occur. For this reason it is desirable to keep the babies under strict supervision.

Although the dosage scheme was calculated on the basis of 100 mg. per lb. (220 mg. per kg.) per day, given in three separate doses, the levels achieved have shown that it is unnecessary for the drug to be given so often, since the serum level is maintained so well. We have therefore employed doses of 33 to 50 mg. per lb. (73 to 110 mg. per kg.) per single dose. An odd feature of this investigation is that the levels obtained were nowhere near so high as those found in older children by Kelly *et al.* (1951) using almost half the dose. It is possible that this discrepancy may be accounted for by the difference in method of assay. That used by Kelly *et al.* was a modification of the Osgood turbidimetric method, whereas ours was a biological assay using a standard β -haemolytic streptococcus as a test organism. Whatever the absolute accuracy and relative merits of the two methods may be, the one used in this series has shown that the levels obtained in the serum were very much greater than those necessary to inhibit chloramphenicol-sensitive pathogens in the test-tube, and all the evidence goes to indicate that this drug is at least as active in the body as *in vitro*.

Our dosage, while rather greater than that recommended by the manufacturers, is very similar to that successfully used by Smellie (1950) in the treatment of infantile gastric enteritis. We feel, therefore, that a dosage of between 33 and 50 mg. per lb. (73 and 110 mg. per kg.), given twice in 24 hours, should be adequate in the treatment of suitable infections in the newborn.

Summary

A haemolytic streptococcus sensitive to 1 µg. of chloramphenicol per ml. was used to assay blood-serum concentrations in 47 newborn babies.

Dosage irrespective of weight proved unsatisfactory in 17 cases.

A scheme of dosage based on body weight was applied to 30 babies, 24 of whom showed satisfactory blood levels for at least 12 hours and detectable levels for 24 hours.

No chloramphenicol was detected in the blood serum in six babies, one of whom had vomited half an hour after its dose. No cause for the remaining five negative results was found. Failure of absorption was discounted, as one of these cases showed a reasonable serum level in a repeat test the following day.

We recommend a dosage as set out in the Table: this represents 33–50 mg. per lb. (73–110 mg. per kg.) per dose, given twice daily.

We would like to thank the paediatricians, paediatric registrars, and nursing staff for their co-operation in this investigation. We are also grateful to Messrs. Parke Davis for generous supplies of chloramphenicol.

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SUMMER HAY-FEVER AND ASTHMA TREATED WITH ANTIHISTAMINIC DRUGS

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In the early summer of 1948 a trial of a new antihistaminic drug was carried out in the hay-fever clinic. It has since been named chlorcyclizine hydrochloride ("histanin"). Each tablet contains 25 mg. of N-methyl-N-(4-chlorobenzhydryl) piperazine dihydrochloride. After this trial it was suggested (Frankland, 1949) that, although antihistamines could help the mild case of hay-fever, they might precipitate the onset of asthma in the more severe cases. This was commented on in the review of hay-fever literature for 1949 (Kaplan and Ehrlich, 1951). It was, however, pointed out that a statistical survey of hay-fever patients treated with antihistamines must be carried out before it could be taken as proved that asthma was more apt to occur in such patients. It is interesting that in another trial (Gay *et al.*, 1948) the high incidence of asthma in hay-fever patients treated with antihistamines had been noted, but not commented upon. There is now fairly widespread belief that hay-fever patients who receive antihistaminic drugs as the only form of therapy are more liable to develop asthma than those who receive no treatment (*British Medical Journal*, 1952).

An experiment was designed to test not only the efficacy in hay-fever and hay-asthma of an untried antihistaminic drug, but also whether there was any statistical difference in the incidence of asthma in treated and untreated hay-fever patients. In the first enthusiasm

that greeted the preparation of many new antihistaminic drugs, the published reports suggested that antihistamines do benefit many cases of asthma. Southwell (1948) commented on the non-critical assessments in many of the published papers from France and America. He concluded as a result of a trial of mepyramine maleate ("anthisan," pyranisamine maleate, or "neo-antergan") in the treatment of asthma that it "conferred no apparent benefit upon 25 specially selected and carefully observed asthmatic patients." Hunter and Dunlop (1948) also concluded that mepyramine maleate was of no value in the prevention of asthma. Frankland (1952) and Watkins (1952) agree with these views.

Scheme of Trial and Methods of Assessment

The patients were treated with three different kinds of tablets: (1) mepyramine maleate, which has had extensive trials and clinical use; (2) a new antihistaminic preparation which has as yet no name and will be referred to as 405-c-49 (chemically it is 3-pyrrolidino-1-(4'-chlorophenyl)-1-(2-pyridyl) prop-1-ene maleate); and (3) inert tablets. It was considered essential that the box of tablets given by the doctor to the patient should be numbered and not named. The consecutive-numbered boxes were given to the patients in the order they reported. Previously the three kinds of tablets had been allocated to the numbered boxes by use of a random-number table. Twin girls who both received the same tablets were the only exception to this random distribution. Anthisan (mepyramine maleate) is normally coloured green, but for the purposes of the trial Messrs. May & Baker kindly supplied white tablets. The inert tablets, which contained 5 gr. (0.32 g.) of lactose, looked similar to but differed in taste from the antihistamine under trial. Each tablet of 405-c-49 contained 10 mg. of the antihistaminic drug, which was thought to correspond clinically to a dose of the 100-mg. tablet of mepyramine maleate. The doctor did not know which type of tablet he gave to the patient (except for the few patients who asked for a change of tablet). It was not until all the results of treatment had been tabulated that the kind of preparation used was entered on the card. Each patient was given a chart and asked to keep a daily record, from the time the symptoms of hay-fever began, of the number of tablets taken each day, and whether the results were good, moderate, or poor so far as the hay-fever was concerned. The letters G, M, and P were used to designate the daily result of taking the tablets.

The patients were told that they were taking part in a trial of a new drug for hay-fever, and that it was believed that the side-effects, if any, would probably not be annoying, but that the dose was not known. It was suggested that up to four tablets a day was probably the correct dose for relief of symptoms, but more or fewer tablets might be necessary. As a third of all patients were to receive inert tablets when first seen, all of them were told that if they thought the tablets given to them were not effective they could either come back for a stronger tablet or use any other preparation that was considered from previous years' treatment to be more effective.

Normally a patient used the same tablet throughout the hay-fever season, though a few patients who were seen more frequently were given the chance of a change of tablet if they so desired. If a patient did ask for a change of tablet, in each case the new antihistaminic tablet 405-c-49 was given. This allowed a direct comparison with either the inert or the mepyramine maleate tablets. In practice only a few patients came back for what was euphemistically called the stronger tablet.

When the patients were first seen at the beginning of the trial they were accepted as suitable for it so long as their complaint was one of seasonal hay-fever. Before the diag-